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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,164	04/04/2005	Susanne Binder	34157-707.831	5602

21971 7590 10/28/2008

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EXAMINER	
KIM, TAEYOON	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
10/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,164	BINDER ET AL.	
	Examiner	Art Unit	
	TAEYOON KIM	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,43,45-49 and 53-61* is/are pending in the application.

4a) Of the above claim(s) *60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,43,45-49,53-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 42, 43, 45-49 and 53-61 are pending.

Response to Amendment

Applicant's amendment and response filed on 7/8/2008 has been received and entered into the case.

Claims 1-41, 44 and 50-52 have been canceled, claim 60 has been withdrawn from consideration as being drawn to non-elected subject matter, and claims 42, 43, 45-49, 53-59 and 61 have been considered on the merits. All arguments have been fully considered.

The declaration filed on 7/8/2008 under 37 CFR 1.131 has been considered but is ineffective to overcome the Young reference.

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Young et al. reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The declarations by Dr. Binder and also separately by Dr. Tseng presented in the current amendment indicate that the conception of the claimed invention was before August 2001, which is apparently prior to the publication of prior art. However, this statement does not have any supporting proof or evidence to confirm the conception prior to August 2001. Therefore, the declaration is ineffective to overcome the claim

rejection under 35 U.S.C.§102(e) based on Young et al.

In the response to the claim rejections under 35 U.S.C.§103 based on Young et al. or Young et al. in view of Grueterich et al. or Young et al. in view of Tseng, applicant relied on the declaration under C.F.R.§1.131 arguing that the subject matter of the claimed invention is prior to the effective date of Young et al. and Grueterich et al. As discussed above, the declaration is insufficient to antedate the current invention prior to the effective date of Young et al. Therefore, the claim rejections are still maintained.

In the response to the claim rejections under 35 U.S.C.§103 based on Liu in view of Dutt et al. in further view of Dua et al. and Young et al. and also in further view of Grueterich et al., applicant states that a 4-way or 5-way combination of art is evidence in itself of non-obviousness. This is not persuasive. Reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Furthermore, applicant argued that a skilled artisan would not have been motivated to replace the collagen substrate of Liu with the amniotic membrane of Dutt et al. because the amniotic membrane of Dutt et al. is incapable of achieving confluent RPE cells or confluent RPE equivalent cells on the membrane. Applicant further asserted that the definition given by the examiner is novel different from "ordinary" meaning of the term "confluent". This is not persuasive. According to Merriam-Webster On-line dictionary, the definition of “confluent” is “flowing or coming together” and in cell culture, when cells contact each other in their growth, they are considered as confluent. In fact, it is not necessary for the term “confluent” to mean "covering entire area of

culture plate or dish" as applicant interpreted. According to the definition disclosed in US 40 C.F.R.§141.2 (http://law.justia.com/us/cfr/title40/40-22.0.1.1.3.1.16.2.html) (p.2), "confluent growth" means a continuous bacterial growth covering entire filtration area of a membrane filter, or a portion thereof, in which bacterial colonies are not discrete. The same definition is applicable to mammalian cell growth. Cells can grow in confluent state locally as well as entirely covering the whole culture plate, dish or membrane.

It is reminded that the current invention does not require growing RPE cells on the amniotic membrane to achieve confluent cells covering entire surface of the membrane. Rather it requires confluent RPE or PRE-equivalent cells cultured on the amniotic membrane. Clearly the confluence of cells on a substrate is dependent on the number of cells initially seeded and the duration of proliferation of the seeded cells. The confluence of the cells can be achieved by simply plate (seed) the cells in the amount sufficiently cover the entire substrate. Thus, it would have been obvious for a person of ordinary skill in the art to seed RPE on the amniotic membrane with the amount to cover entire surface of the membrane. By doing so, the further manipulation of culturing RPE cells is not necessary, reducing potential complications which might occur during the culturing process including contamination.

Although Dutt et al. indicate that amniotic membrane has less potent compared to collagen in the proliferation rate of RPE, but it does not mean that RPE cannot grow or adhere to the substrate. The "inhibitory effect" referred by Dutt et al. is not that the amniotic membrane prevents the growth of RPE cells, rather it is meant that the proliferation of RPE cells on the amniotic membrane is less than RPE cells grown on

collagen or plastic culture dishes. In fact, the number of RPE cells after 21 days of culturing on the amniotic membrane (0.86±0.09) is higher than the initial number of cells seeded on day 1 (0.27±0.03) according to Table 2 of Dutt et al. Although the fold increase over the period of culturing RPE cells grown on the amniotic membrane is less than those grown on the tissue culture plastic or collagen IV-coated substrate, this cannot be interpreted as "incapable" of amniotic membrane achieving confluent RPE cells on the membrane. As discussed above, RPE cells can be seeded in higher number capable of yielding enough number of cells in a short period of culturing duration to cover the given surface of the membrane, or at the amount which covers the entire surface of the membrane.

Thus, the number of cells seeded on the amniotic membrane can be routinely modified, and it would be desired for a person of ordinary skill in the art to have sufficient number of cells seeded on the membrane to cover entire membrane surface in order to use the RPE cells in a method of treating a retinal disease of Liu without further manipulation including longer culturing of the cells. Liu teaches to obtain a confluent monolayer of RPE cells in the method of treating a retinal disease, and the confluent cells can be obtained by plating a sufficient number of cells to cover the entire surface of the membrane as discussed above. Thus, it would be obvious to a person of ordinary skill in the art to plate RPE cells in a sufficient number to cover entire surface of the amniotic membrane for the method of Liu et al. in view of Dutt et al.

Therefore, the claim rejections under 35 U.S.C.§103 based on Liu in view of Dutt et al. in further view of Young et al. and Grueterich et al. are still maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 42, 45, 47-49, 54, 59 and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by Young et al. (WO 03/018040 A1) in light of Dua et al. (Br. J. Ophthalmol. 1999) or Tseng (US 6,152,142; IDS ref. #1).

Young et al. teach a method and a composite graft for the treatment of conditions associated with photoreceptor loss (e.g. age-related macular degeneration), where the composite graft comprising RPE cells grown on base membrane such as amniotic membrane (see abstract and p.12 lines 2-14). Young et al. also teach other types of cells including precursor to RPE cells or retina stem cells (see p.5, lines 10-14 and 18-19). Young et al. teach that the graft can be delivered to the subretinal space (see p.17, lines 7-8).

With regard to the term "confluent", since it does not define the amount of confluence (e.g. 50% or 100%, etc.), the term is considered as any percentage of confluence for RPE cells.

With regard to the limitation of the presence of "pharmaceutically active molecule" in the composite of the method, it is considered that the limitation of

"pharmaceutically active molecule" is an inherent property of the amniotic membrane of Young et al. as supported by Dua et al. Dua et al. teach that the amniotic membrane produces various growth factors such fibroblast growth factor (see p.748, right column, a section under the title of "Amniotic membrane in ophthalmology"). Fibroblast growth factor is considered to be a therapeutic drug. Furthermore, Young et al. teach the substrate (e.g. amniotic membrane) can also serve as a particularly convenient delivery system for angiogenic/anti-angiogenic agents (therapeutic drugs) or other bioactive agents including (see p.12, lines 18- p.13, line 3).

Although Young et al. do not particularly teach the intact amniotic membrane having a basement membrane and a stroma, Tseng teaches that an amniotic membrane comprises two major components: the basement membrane and stroma (see col. 1, lines 23-24). Therefore, the amniotic membrane of Young et al. inherently comprises basement membrane and stroma.

Thus, the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42, 43, 45-49, 57-59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al. (supra).

Young et al. teach a method and a composite graft for the treatment of conditions

associated with photoreceptor loss (e.g. age-related macular degeneration), where the composite graft comprising RPE cells grown on base membrane such as amniotic membrane (see abstract and p.12 lines 2-14). Young et al. also teach other types of cells including precursor to RPE cells (see p.5, lines 18-19). Young et al. teach that the graft can be delivered to the subretinal space (see p.17, lines 7-8). Young et al. also teach the membrane substrate can also serve as a particularly convenient delivery system for various bioactive agents (pharmaceutically active agents) such as growth factors (see p.12, line 18 through p.13, line 3).

Although Young et al. is silent in the concentration of RPE cells being confluent or 16,000 to about 20,000 per 4 mm^2 of amniotic membrane, the concentration of RPE cells required for the graft taught by Young et al. would be considered as a result-effective variable. As such, the variables would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d

at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the :references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

With regard to the limitation of "human amniotic membrane" in claim 46, Young et al. do not particularly teach the source of the amniotic membrane. However, since Young et al. disclose the base membrane can be autologous to a patient, and it would have been obvious to a person of ordinary skill in the art to use human amniotic membrane for human patients.

With regard to the limitation in claims 57 and 58 drawn to the use of excimer laser, Young et al. do not particularly teach the limitation. However, it would have been obvious to a person of ordinary skill in the art to try excimer laser to trim and/or modify the base membrane suitable for transplantation because the excimer laser ablation

technique is well known in the art to cut and reshape variety of tissues and laser treatment is commonly used for eye diseases as numerously disclosed in Young et al. (e.g. p.2, line 18). Since the technique is readily available in the art, and a person of ordinary skill in the art would recognize the technique suitable for modifying amniotic membrane, a person of ordinary skill in the art would choose to use the excimer laser technique in place of the surgical instrument for cutting the substrate for transplantation.

The Supreme Court recently states in KSR v. Teleflex (550 US82 USPQ2d 1385, 2007) "The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

The limitation of claim 58 is considered as a result of the method step in claim 57. Claim 58 contains a "wherein" clause that merely states the result of the limitations in the claim and therefore, adds nothing to the patentability or substance of the claim. Therefore, this phrase does not limit the claim. See *Texas Instruments Inc. v. International Trade Commission*, 26 USPQ2d 1010 (Fed. Cir. 1993); *Griffin v. Bertina*, 62 USPQ2d 1431 (Fed. Cir. 2002); *Amazon.com Inc. v. Barnesandnoble.com Inc.*, 57

USPQ2d 1747 (Fed. Cir. 2001).

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al. (supra) in view of Grueterich et al. (2002; IDS ref. #28).

Claim 53 is drawn to a limitation to the amniotic membrane being epithelially denuded.

Young et al. render the subject matter of claim 42 obvious (see above).

Young et al. do not teach the amniotic membrane being epithelially denuded.

Grueterich et al. teach the use of epithelially denuded amniotic membrane in culturing limbal epithelium (see whole document; p.64, Materials and Method).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use epithelially denuded amniotic membrane of Grueterich et al. in the method of Young et al.

The skilled artisan would have been motivated to make such a modification because both intact and epithelially denuded amniotic membrane would be suitable for support of epithelial cell culture. Since amniotic membrane is a suitable substrate for culturing not only corneal epithelial cells as taught by Grueterich et al. but also for RPE cells, a person of ordinary skill in the art would have considered the choice of intact or denuded amniotic membrane as a routine optimization procedure to obtain optimal environment for culturing RPE cells for treating a retinal disorder.

Therefore, the invention as a whole would have been prima facie obvious to a

person of ordinary skill at the time the invention was made.

Claims 54-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al. (supra) in view of Tseng (supra).

Young et al. teach the limitations of claim 42 (see above).

Although Young et al. do not particularly teach the intact amniotic membrane having a basement membrane and a stroma, Tseng teaches that an amniotic membrane comprises two major components: the basement membrane and stroma (see col. 1, lines 23-24). Therefore, it would have been obvious to a person of ordinary skill in the art that the amniotic membrane of Young et al. inherently comprises basement membrane and stroma.

Young et al. do not teach a step of adding mesenchymal cells to the stroma of the amniotic membrane or the mesenchymal cells being fibroblasts.

Tseng teaches that when fibroblasts (mesenchymal cells) are grown in the stromal side of amniotic membrane, it provides an environment comparable to isolated collagen (fibroblasts are collagen-producing cells) and better cell growth in culture than a plain plastic surface.

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to add fibroblasts on the stromal side of the amniotic membrane of Young et al.

The skilled artisan would have been motivated to make such a modification because Tseng teaches an advantage given by the fibroblast culture on the stromal side of the amniotic membrane providing better cell culture environment for epithelial cells

(see col. 4).

With regard to the limitation in claims 57 and 58 drawn to the use of excimer laser, Young et al. do not particularly teach the limitation. However, it would have been obvious to a person of ordinary skill in the art to try excimer laser to trim and/or modify the base membrane suitable for transplantation because the excimer laser ablation technique is well known in the art as supported by Tseng (e.g. col. 3, line 19) to cut and reshape variety of tissues and laser treatment is commonly used for eye diseases as numerously disclosed in Young et al. (e.g. p.2, line 18). Since the technique is readily available in the art, and a person of ordinary skill in the art would recognize the technique suitable for modifying amniotic membrane, a person of ordinary skill in the art would choose to use the excimer laser technique in place of the surgical instrument for cutting the substrate for transplantation.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 42, 43, 45-46, 49, 54, 57-59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu (US 6,045,791; IDS reference #7) in view of Dutt et al. (1991; IDS ref. #15) in further view of Dua et al. (supra) and Young et al. (supra).

Liu teaches a method of treating a retinal disorder such as age-related macular degeneration, by transplanting retinal pigment epithelium (RPE) cells cultured on an attachment substrate into the subretinal area of a patient in need thereof (see Abstract and column 7, lines 57-59 and 65-67; Example 1).

Liu does not teach the use of amniotic membrane.

Dutt et al. teach the use of human amniotic membrane as a substrate for culturing retinal pigment epithelial cells (see whole document).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to replace the collagen substrate of Liu with the amniotic membrane of Dutt et al. in the method of Liu.

The skilled artisan would have been motivated to make such a modification because both the substrate of Liu and the amniotic membrane of Dutt et al. are used for the growing RPE cells, they are considered as a suitable alternative or equivalent for growing RPE cells for transplantation.

With regard to the argument based on inferior property of the amniotic membrane compared to the collagen substrate taught by Dutt et al., teaching away to use the amniotic membrane over the collagen, although the amniotic membrane is less effective in proliferating RPE cells over the collagen substrate, it is recognized by a person of ordinary skill in the art that the amniotic membrane can be used for the same purpose as the collagen substrate. M.P.E.P. §2145 states "A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (Claims were directed to an epoxy resin based printed circuit material. A prior art reference disclosed a polyester-imide resin based printed circuit material, and taught

that although epoxy resin based materials have acceptable stability and some degree of flexibility, they are inferior to polyester-imide resin based materials. The court held the claims would have been obvious over the prior art because the reference taught epoxy resin based material was useful for applicant's purpose, applicant did not distinguish the claimed epoxy from the prior art epoxy, and applicant asserted no discovery beyond what was known to the art.).

Furthermore, the skilled artisan would have been motivated to replace collagen of Liu with the amniotic membrane of Dutt et al., because it is well known in the art that amniotic membrane is used for treating eye diseases as supported by Dua et al. Dua et al. teach the amniotic membrane serves as a transplanted basement membrane which facilitates migration of epithelial cells, and further the presence of various growth factors in the amniotic membrane can stimulate epithelization (see p.748 under "Amniotic membrane in ophthalmology"). Still further Young et al. teach that the amniotic membrane is an equivalent for the Bruch's membrane (see abstract and p.12 lines 2-14). Thus, a person of ordinary skill in the art would recognize the amniotic membrane as an equivalent to the Bruch's membrane, which is a natural substrate for RPE cells in vivo.

Although Liu in view of Dutt et al. in further view of Dua et al. and Young et al. do not particularly teach the number of cells on the amniotic membrane, however, because the number of cells used in the claimed method is considered as one of result effective variables. The variables would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references. Generally, differences in

concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the :references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

With regard to the limitation of the presence of "pharmaceutically active molecule" in the composite of the method, it is considered that the limitation of "pharmaceutically active molecule" is inherently accomplished by the use of amniotic membrane of Dutt et al. in the method of Liu. Because Dua et al. teach the amniotic membrane produces various growth factors such fibroblast growth factor (see p.748, right column, a section under the title of "Amniotic membrane in ophthalmology").

Although Liu in view of Dutt et al. in further view of Dua et al. and Young et al. do not particularly teach the use of excimer laser ablation technique, since it is necessary to cut the substrate, having RPE cells grown on it, for transplantation as described in Liu (see Example 1, column 11, lines 10-11), and excimer laser ablation technique is well known in the art to cut and reshape variety of tissues, it would have been obvious for a person of ordinary skill in the art to optimize the cutting procedure by using a technique with high precision such as excimer laser ablation technique. Further, a surgical instrument used in the method of Liu for cutting the substrate containing RPE cells and excimer laser ablation would be considered as art-recognized equivalents, and therefore, the excimer laser ablation would be used in place of the surgical instrument for cutting the substrate for transplantation.

The limitation of claim 58 is considered as a result of the method step in claim 57. Claim 58 contains a "wherein" clause that merely states the result of the limitations in the claim and therefore, adds nothing to the patentability or substance of the claim. Therefore, this phrase does not limit the claim. See *Texas Instruments Inc. v. International Trade Commission*, 26 USPQ2d 1010 (Fed. Cir. 1993); *Griffin v. Bertina*,

62 USPQ2d 1431 (Fed. Cir. 2002); *Amazon.com Inc. v. Barnesandnoble.com Inc.*, 57 USPQ2d 1747 (Fed. Cir. 2001).

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu (supra) in view of Dutt et al. (supra), in further view of Dua et al. (supra), Young et al. (supra) and Grueterich et al. (2002; IDS ref. #28).

Liu in view of Dutt et al. in further view of Dua et al. and Young et al. render the subject matter of claim 42 obvious (see above).

Liu in view of Dutt et al. in further view of Dua et al. and Young et al. do not teach the amniotic membrane being epithelially denuded.

Grueterich et al. teach the use of epithelially denuded amniotic membrane in culturing limbal epithelium (see whole document; p.64, Materials and Method).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use epithelially denuded amniotic membrane of Grueterich et al. in the method of Liu in view of Dutt et al. in further view of Dua et al. and Young et al.

The skilled artisan would have been motivated to make such a modification because both intact and epithelially denuded amniotic membrane would be suitable for support of epithelial cell culture. Since amniotic membrane is a suitable substrate for culturing not only corneal epithelial cells as taught by Grueterich et al. but also for RPE cells, a person of ordinary skill in the art would have considered the choice of intact or

denuded amniotic membrane as a routine optimization procedure to obtain optimal environment for culturing RPE cells for treating a retinal disorder.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu (supra) in view of Dutt et al. (supra), in further view of Dua et al. (supra) Young et al. (supra) and Tseng (supra).

Liu in view of Dutt et al. in further view of Dua et al. and Young et al. render the subject matter of claim 42 obvious (see above).

Liu in view of Dutt et al. in further view of Dua et al. and Young et al. do not teach a step of adding mesenchymal cells to the stroma of the amniotic membrane or the mesenchymal cells being fibroblasts.

Tseng teaches that when fibroblasts (mesenchymal cells) are grown in the stromal side of amniotic membrane, it provides an environment comparable to isolated collagen (fibroblasts are collagen-producing cells) and better cell growth in culture than a plain plastic surface.

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to add fibroblasts on the stromal side of the amniotic membrane of Liu in view of Dutt et al. in further view of Dua et al. and Young et al.

The skilled artisan would have been motivated to make such a modification because Tseng teaches an advantage given by the fibroblast culture on the stromal side of the amniotic membrane providing better cell culture environment for epithelial cells.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAEYOON KIM whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 4:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Taeyoon Kim